
Analytical strategy to obtain information on less-studied compounds

6th EFSA FCM network
11 July 2018

Gilles RIVIERE
ANSES

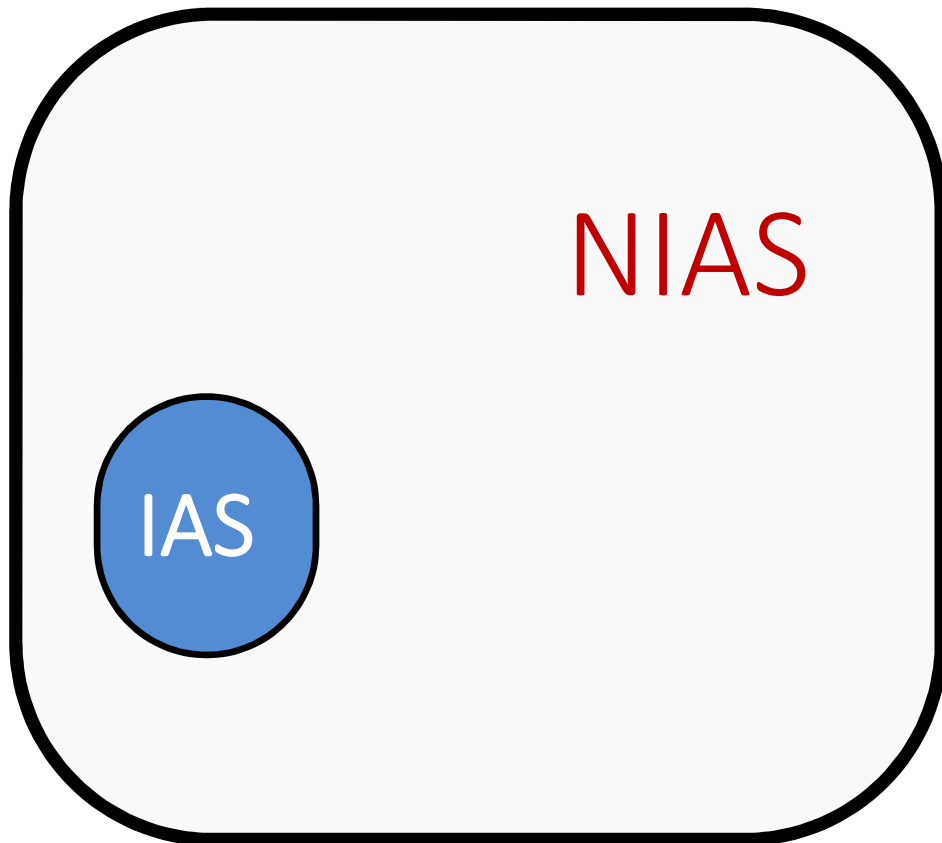
Thesis work (Eelco Nicolaas Pieke)



- 1°) Identification of unknown contaminants migrating from paper and board
- 2°) Risk prioritization of substances

Constituents of food contact materials

IAS are only a fraction of the total number of chemicals in FCM



Non-intentionally added substances

(NIAS):

- Mostly **unknown**
- Mostly no authorization
- Virtually unlimited in number

Research focus

- Paper and board FCM:

- Widely used
- Poorly regulated
- Best case: national legislation



- Known: <3 000 compounds in paper and board, printing inks and coatings
- Expected: >10 000 compounds; possibly **more**
- **Paper and board used as a case study**

Test conditions for paper / board

- There are **no agreed test conditions** for paper / board
- ... but they do exist for plastics



- Paper is semi-permeable; plastic is not
- Paper contact use is generally shorter
- Paper is rarely reused except for recycling

Analysis issues for migration from FCM

- Acquisition of data is generally based on **targeted principles**
 - Relies on prior knowledge of the constituents
 - Concentrates on a small number of targets
 - Strongly relies on reference standards
- This **works fine** for the well-defined IAS!
- This **does not work** for NIAS!



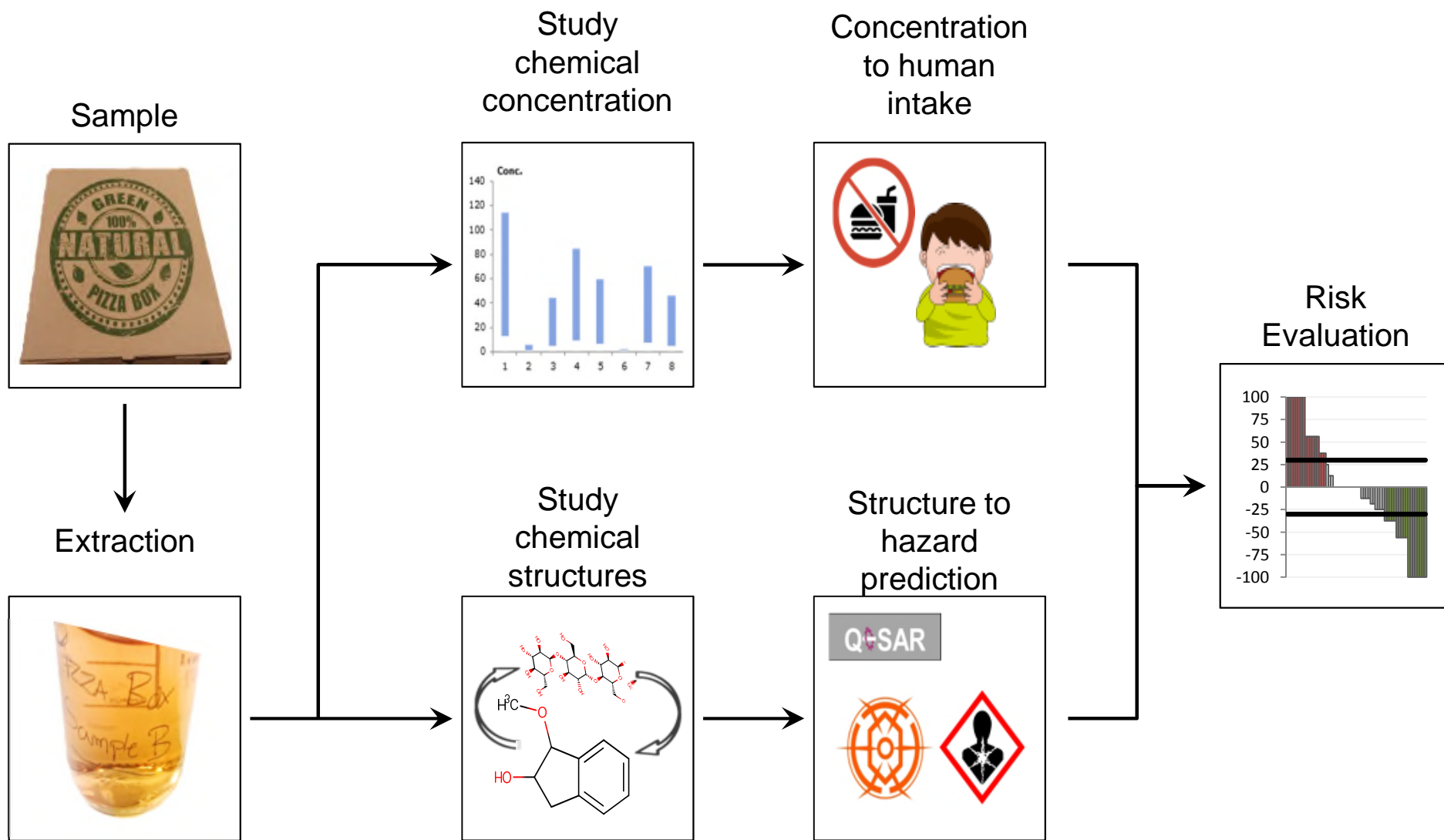
The problem with the current solution

There are NIAS in food due to FCM. These need to be **risk assessed**.

- 1) To focus on the most dangerous compounds, specific data is needed
 - **Data** is needed to define **Priority**

- 2) Targeted studies need to know which compound to look at
 - **Priority** is needed to obtain **Data**

Development of exploration strategies



Moving forward with tentative data

What is
there?

How much
is there?

Analysis of FCM extracts

- Extracting information on possibly unknown compounds
- UHPLC – Ultra High Performance Liquid Chromatography
- ESI – Electrospray Ionization
- QTOF – Quadrupole Time of Flight



- + Separation power: UHPLC x2
- + Optimised for screening

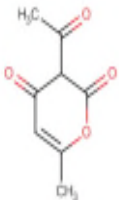
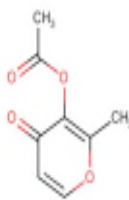
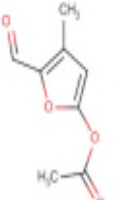
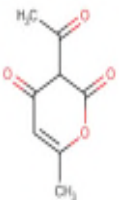


Moving forward with tentative data

What is there?

- MS/MS → no information on real structure

➔ MS fragments compared to 4 databases

DB#1			DB#2			DB#3			DB#4		
Formula	Structure	Score	Formula	Structure	Score	Formula	Structure	Score	Formula	Structure	Score
$C_8H_8O_4$		75.5	$C_8H_8O_4$		76.1	$C_8H_8O_4$		78.6	$C_8H_8O_4$		75.5

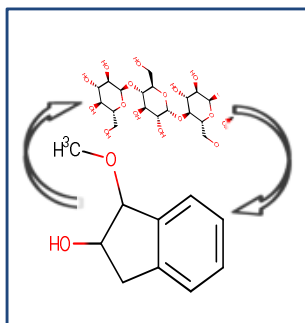
- Predictions are **suggestions**: not entirely accurate
- Improvement: use multiple databases
- The actual structural is likely “somewhere in between”

Moving forward with tentative data

What is there?



Structure suggestions



Moving forward with tentative data

How much
is there?

- Surrogate use as quantify marker
- Surrogate with similar properties as the Analyte
- 1 Surrogate for 1 Analyte

Prediction error:
1.1-fold to 3-fold

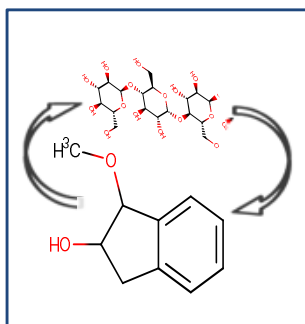
5 $\mu\text{g/L}$ ← True conc. 15 $\mu\text{g/L}$ → 45 $\mu\text{g/L}$

Moving forward with tentative data

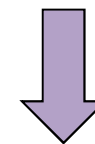
What is there?



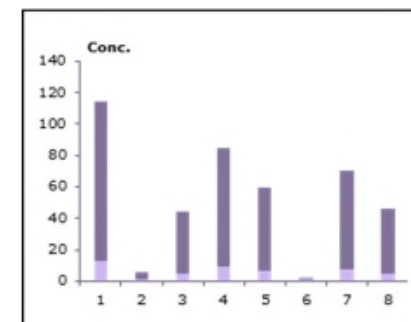
Structure suggestions



How much is there?



Concentration estimates

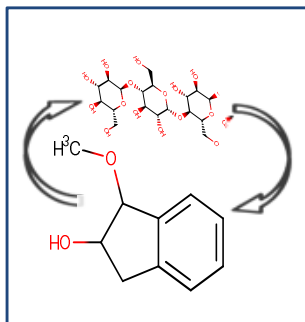


Moving forward with tentative data

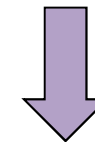
What is there?



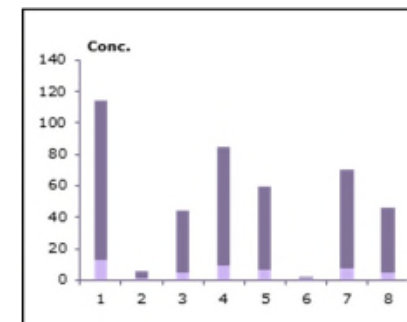
Structure suggestions



How much is there?



Concentration estimates



Risk estimation

Risk prioritization based on tentative data

How to translate tentative data into risk priority?

$$\text{Risk}_{est} = f(\text{Exposure}_{est}, \text{Hazard}_{est})$$



Semi-quant.



QSAR
predictions:
Overall hazard
likeness

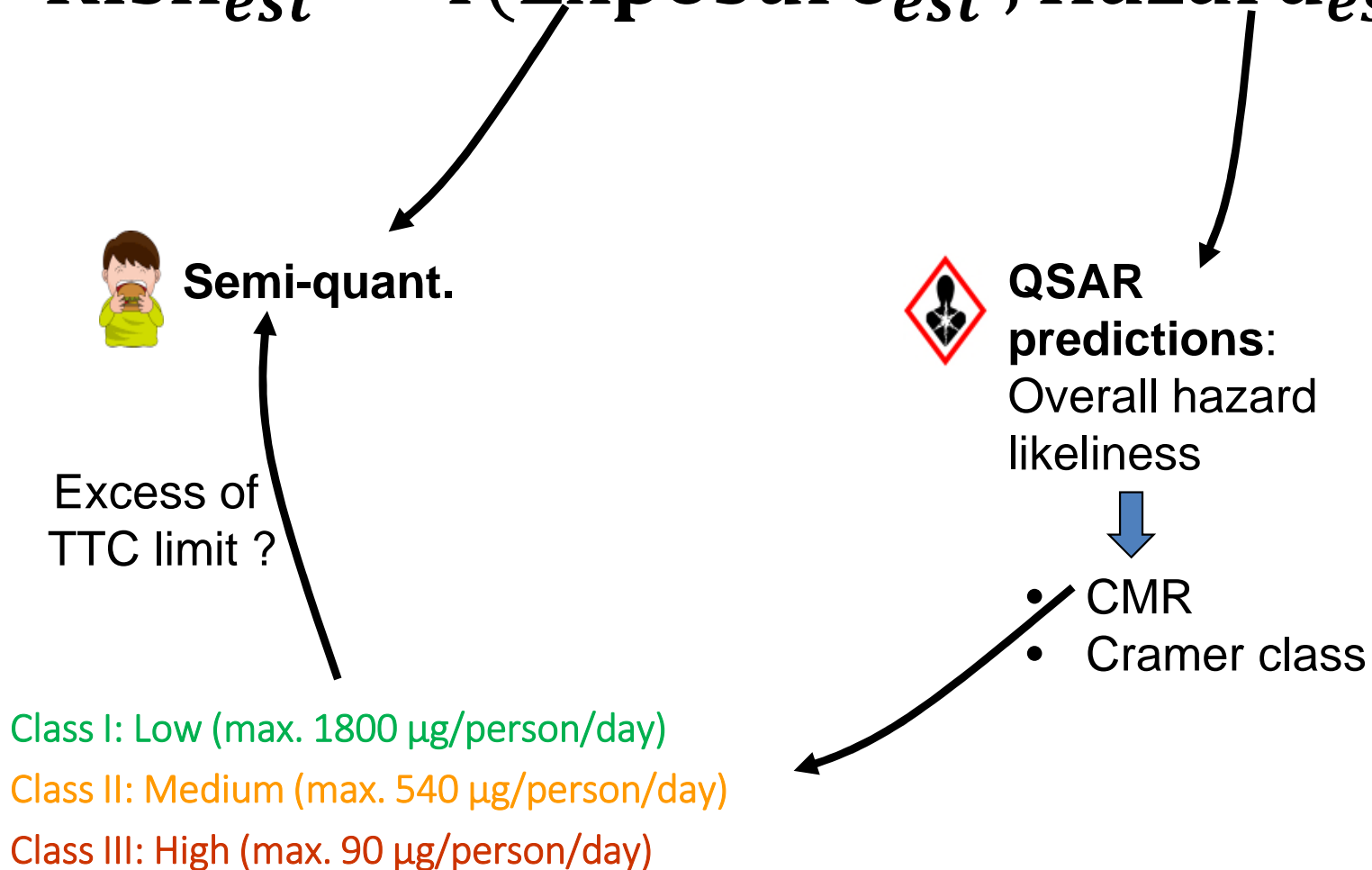


- CMR
- Cramer class

Risk prioritization based on tentative data

How to translate tentative data into risk priority?

$$\text{Risk}_{est} = f(\text{Exposure}_{est}, \text{Hazard}_{est})$$



Risk prioritization based on tentative data

Requires **more** than just a calculation

- Structures
- Exposure
- QSAR: **CMR**

For 1 discovered compound

Source	Predicted structure:	Score:	TTC excess	C	M	R
Internal database		78.2	29%	-0.38	-0.66	+0.43
REACH database		76.5	576%	-0.31	-0.87	+0.42
Agilent DB		78.2	29%	-0.38	-0.66	+0.43
ChemSpider		82.8	576%	+0.69	+0.54	+0.27
PubChem		78.0	29%	-0.39	-0.39	-0.37

Risk prioritization based on tentative data

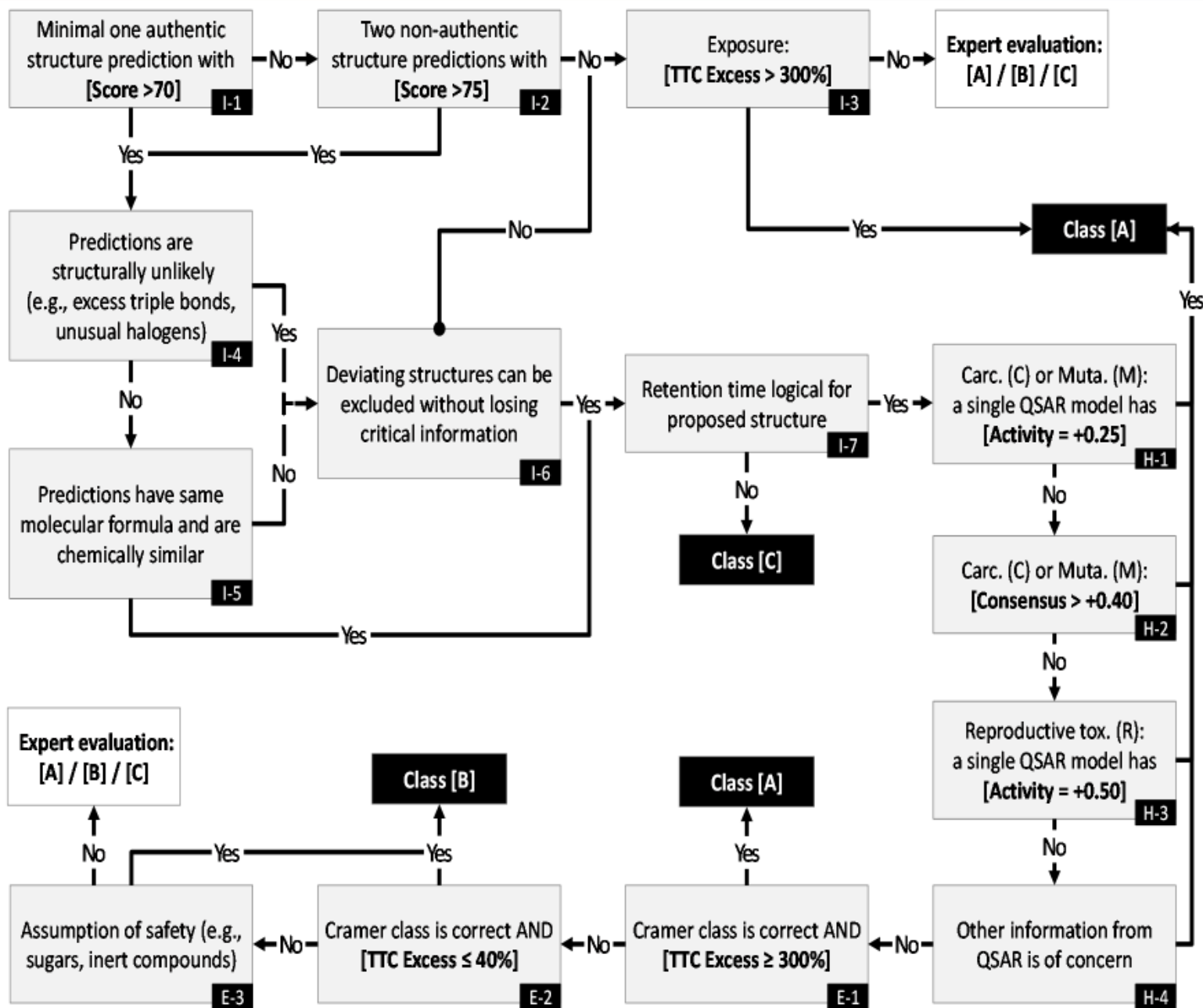
- Development of a hybrid decision model
 - One part data-driven
 - One part expert-driven

Some decisions
can be based
on **rules**

Some must rely on
the assessors' built
expertise

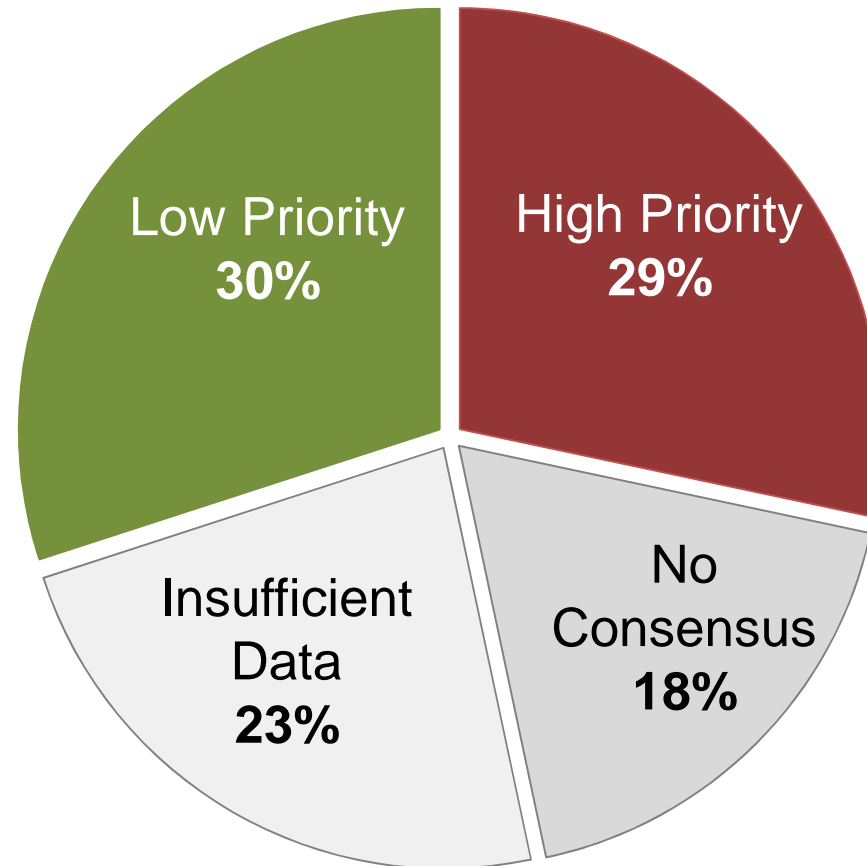


Risk prioritization based on tentative data



Risk prioritization based on tentative data

- 60 selected compounds
- 4 assessors that decide : **high risk**, **low risk**, incomplete information



Conclusion

- ❑ Risk assessment of substances is slow and costly
- ❑ A risk prioritization tool was developed (data and expert driven)
- ❑ Early stage prioritization based on data from exploration experiments
- ❑ Automated decision to improve the capacity of the tool to more compounds